American Journal of Medical Genetics 68:476–480 (1997)

Proximal Partial 5p Trisomy Resulting From a Maternal (19;5) Insertion

Isabel Lorda-Sánchez,[1,2*] Miguel Urioste,[3] Amelia Villa,[2] María del Carmen Carrascosa,[4] Maria Socorro Vázquez,[4] Andrés Martínez,[4] and María Luisa Martínez-Frías[1,2]

[1]*Departamento de Farmacología, Facultad de Medicina, Universidad Complutense, Madrid, Spain*
[2]*ECEMC, Facultad de Medicina, Universidad Complutense, Madrid, Spain*
[3]*ECEMC and Hospital Universitario San Carlos, Madrid, Spain*
[4]*Servicio de Neonatología, Hospital General de Albacete, Albacete, Spain*

We present a case with a partial duplication 5p11→5p13.3 resulting from a maternal ins (19,5)(p11;p11-p13.3). The diagnosis was confirmed by FISH and complement component determinations. The clinical picture was similar to those described in patients with complete duplication of the short arm and in some patients with partial 5p duplications, affecting at least band 5p13. A special significance of band 5p13 in the clinical severity of 5p duplications is discussed. Am. J. Med. Genet. 68:476–480, 1997.

KEY WORDS: 5p11-p13.3 duplication; C6; C7; C9; complement components; interchromosomal insertion; partial 5p trisomy; FISH; chromosomal abnormality

INTRODUCTION

The first descriptions of duplication 5p [Lejeune et al., 1964] were followed by over 40 reported cases, mostly involving only the distal part of the short arm. The cases with 5p duplications affecting the whole arm share a clinical picture whose main findings include: macrocephaly with prominent occiput, facial anomalies characterized by upslanted palpebral fissures with hypertelorism and epicanthus, depressed nasal bridge, midface hypoplasia, micrognathia, and dysplastic ears. Other common defects are short neck, club feet, abdominal muscles hypoplasia, heart defects, feeding and respiratory difficulties, and anomalies of the central nervous system with dilated cerebral ventricles and hydrocephaly as frequent complication. The infants also show generalized hypotonia with seizures and psychomotor retardation. Failure to thrive and recurrent respiratory infections often cause an early death.

A similar clinical picture has been found in some cases with partial 5p duplications [Vowles et al., 1984; Kleczkowska et al., 1987; Rethoré et al., 1989; Leichtman et al., 1991] in contrast to some others with only mild phenotypic findings [Chia et al., 1987; Webb et al., 1988; Zenger-Hain et al., 1993; Chen et al., 1995]. To explain the variable clinical severity of partial 5p trisomies, the extent of the trisomic chromosomal segment [Zabel et al., 1978], as well as the specificity of the band involved [Chia et al., 1987], have been postulated.

As far as we know, no duplication of the proximal region only, from centromere to 5p13, has been reported previously. Here we present a case with a partial duplication 5p11→5p13.3 resulting from a maternal insertion (19,5)(p11;p11–p13.3), whose clinical picture is similar to that described in patients with complete duplication of the short arm.

CLINICAL REPORT

The propositus was ascertained through the Spanish Collaborative Study of Congenital Malformations (ECEMC). He was the product of the first pregnancy of a healthy 29-year-old woman and a nonconsanguineous healthy 29-year-old father. Pregnancy was uneventful. Delivery was complicated by one turn of the umbilical cord around the neck. Birthweight was 2,815 g (25th centile), length 49.5 cm (50th centile), and head circumference 35cm (75–90th centile). Physical examination demonstrated the following craniofacial anomalies: relative macrocephaly with synostosis of the sagittal suture and compensating dehiscence of the remaining sutures, dolichocephaly with frontal bossing and mild hollowing of temporal region, apparently low-set, small, and abnormally modeled ears, horizontal palpebral fissures, mild epicanthus and flat nasal bridge with apparent hypertelorism, short nose, midface hypoplasia, open mouth with full lips, and micrognathia. He showed a bell-shape thorax and an extreme hypoplasia of abdominal muscles. Both feet were clubbed with proximally implanted hallux. The hands showed arachnodactyly. Inspection of the genitalia showed left cryptorchidism (Fig. 1).

Contract grant sponsor: Consejería de Salud de la Comunidad Autónoma de Madrid, Spain.

*Correspondence to: Dra. Isabel Lorda-Sánchez, ECEMC, Facultad de Medicina, Universidad Complutense, E-28040 Madrid, Spain.

Received 22 December 1995; Accepted 18 June 1996

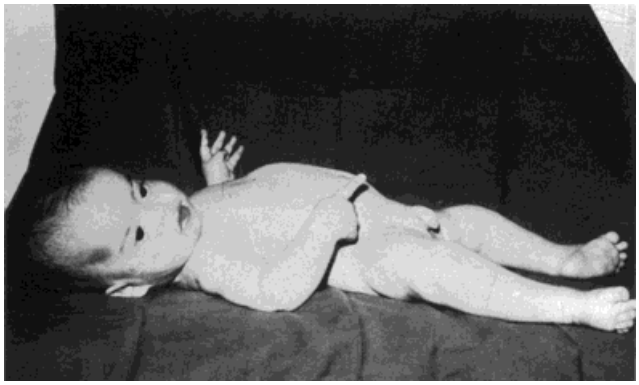

Fig. 1. The patient at 6 months.

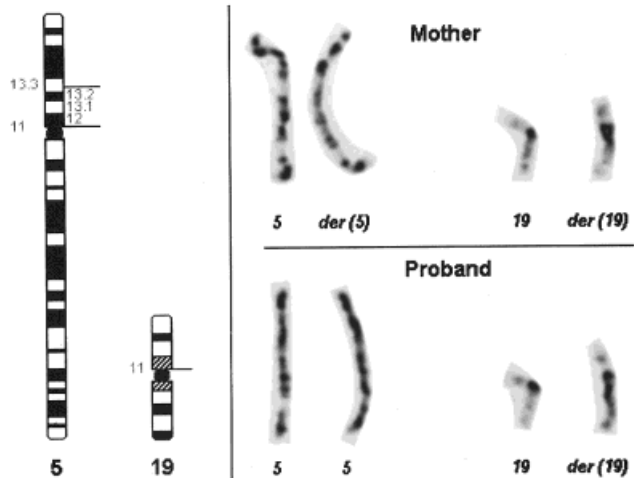

Fig. 2. Idiogram of chromosomes 5 and 19 indicating the breakpoints of the interchromosomal insertion and partial GTG-banded karyotype of mother, showing the insertion, and of the child, who has inherited the der(19) and the normal chromosome 5 from his mother.

He presented slight respiratory distress, secondary to laryngomalacia. Neurologic examination showed hypotonia of the flexor muscles of the neck with tendency to opisthotonos because of the predominance of the extensor muscles. During hospitalization, he experienced seizures, which were controlled with phenobarbital.

An X-ray study of the skull and a cerebral ultrasonography showed synostosis of the sagittal suture and marked dilatation of the lateral cerebral ventricles. A CT scan also demonstrated partial agenesis of the corpus callosum affecting the anterior two-thirds, including the genu. Renal ultrasound was normal and urine and blood metabolic screenings were negative.

CYTOGENETIC STUDIES

Cytogenetic analysis of the propositus' peripheral blood lymphocytes showed a male karyotype with extra chromosome material in the pericentromeric region of the short arm of one chromosome 19. Paternal karyotype was normal, but maternal chromosome analysis showed an insertional translocation involving chromosomes 5 and 19: 46,XX,ins(19;5)(p11;p11p13.3).

The karyotype of the propositus was therefore interpreted as: 46,XY,−19,+der(19)ins(19;5)(p11;p11p13.3) mat. He showed a partial duplication of chromosome 5, apparently bands 5p11→5p13.3, product of a maternal unbalanced insertional translocation (Fig. 2).

FISH analysis with a library for chromosome 5 (COATOSOME total chromosome 5; ONCOR) was performed on chromosome preparations from blood lymphocytes of patient and mother according to manufacturer's instructions. The insertion of material of chromosome 5 on chromosome 19 was confirmed in both cases (Fig. 3).

Other Investigations

In order to determine the implication of band 5p13 in the insertion, the complement components C6, C7 and C9, known to be located on 5p13 [Rogne et al., 1991], were measured by radial immunodiffusion in the plasma of the patient and his parents. The values for C6, C7, and C9 in the patient's plasma were 19.0 mg/dL (control values 4.5–9.6), 7.9 mg/dL (5.5–8.5), and 25.9 mg/dL (7.0–45), respectively. This increase of C6 was not seen in either of the parents, whose values for the three components were normal.

DISCUSSION

The most striking phenotypic findings in the present case are consistent with the clinical picture delineated in patients with complete duplication of the short arm of chromosome 5. As shown in Table I, these findings were also reported in some, but not all, cases with partial 5p duplications.

The variable clinical severity observed in partial 5p trisomy was first related to the length of the duplicated segment [Zabel et al., 1978]. In a later report, Chia et al. [1987] presented a case with a large, distal duplication of 5p (p14→pter) and only mild anomalies, concluding that the severity of the manifestations in 5p duplications was related to the band involved rather than to the length of the duplication. They suggested that the most severe phenotypic effects in cases with dup 5p were due to duplications of the relatively small segment 5p11→5p13. This has been supported by some other reports of mildly affected cases with duplications involving only the distal part of the short arm, 5p14 or 5p15 (group 1 in Table I), as well as some reports of newborn infants with severe clinical findings and poor course, who had more proximal duplications, affecting at least band 5p13 (group 2 in Table I).

As far as we know, the present case is the first one reported with a duplication affecting only the most proximal bands of the short arm of chromosome 5 (5p11→5p13). The duplicated segment overlaps the duplications of some of the reported severe cases only on band 5p13 (groups 2 in Table I), suggesting a special significance of this band in the clinical severity of 5p duplications. Two cases (9 and 11) showed duplications of only the distal part of this band, 5p13.3. Patient 11 reported by Chen et al. [1995] showed only mild affection, except for a congenital adrenal hypoplasia, whereas in patient 9 by Rethoré et al. [1989], the typical

TABLE I. Present and Previous Cases With Partial Duplication 5p Compared to Cases With Complete Duplication

	Group 1[a]			Group 2[b]								Present	Complete
Case	1	2	3	4	5	6	7	8	9	10	11	case	dup5p[c]
Duplicated segment	p14-pter	p14.3-p15.1	p14-p15.3	p13-pter	p13-pter	p13-pter	p13.1-p15.3	p13-p15	p13.32-p14.3	p12-p15.3	p13.3-p15.1	p11-p13.3	p11-pter
Hypotonia			x		x			x	x	x		x	6/6
Ventriculomegaly							x	x				x	4/6
Other brain abnormalities				x		x	x					x	1/6
Seizures/abnormal EEG					x							x	3/6
Psychomotor retardation	Mild	Mild	x	x	x			x	Mild		Mild	x	3/6
Macrocephaly				x	x	x	x	x	x	x		x	6/6
Dolichocephaly			x	x	x		x	x	x			x	3/6
Enlarged ant. fontanelle												x	2/6
Epicanthal folds								x	x	x		x	4/6
Upslanting palpebral fissures					x		x			x			4/6
Hypertelorism							x			x		x	4/6
Microphthalmia/coloboma				x		x			x				0/6
Strabismus				x				x					1/6
Broad/deep nasal bridge			x		x	x		x	x	x		x	5/6
Short nose								x	x			x	4/6
Midface hypoplasia												x	3/6
Macroglossia				x	x	x			x				3/6
High arched palate			x					x		x			2/6
Microretrognathia					x	x	x	x	x			x	5/6
Low set “dysplastic” ears				x	x	x	x	x	x	x		x	6/6
Short neck/redundant skin folds								x	x	x			5/6
Arachnodactyly				x	x	x			x	x		x	0/6
Fifth finger clinodactyly					x			x		x			1/6
Short/prox.implanted first toe												x	2/6
Club feet				x			x	x	x	x		x	4/6
Abdominal muscles hypoplasia/umbilical hernia									x			x	2/6
Congenital heart defect			x			x	x			x			4/6
Respiratory difficulties				x		x		x		x		x	3/6
Recurrent resp. infections				x				x				x	2/6
Low pitched/week cry						x				x			2/6
Short stature	x		x					x			x		2/6
Failure to thrive				x		x			x	x		x	2/6
Early death				31 mos		37 days	1 day			3 mos			4/6

[a] Group 1: patients with distal duplications affecting bands 5p14-5p15: 1-Chia et al., 1987; 2-Webb et al., 1988; 3-Zenger-Hain et al., 1993.
[b] Group 2: patients with duplications affecting at least part of band 5p13 and part of bands 5p14-5p15: 4-Brimblecombe et al., 1977; 5-Zabel et al., 1978; 6-Vowles et al., 1984; 7-Kleczkowska et al., 1987;8-Gustavson et al., 1988; 9-Rethoré et al., 1989; 10-Leichtman et al., 1993; 11-Chen et al., 1995.
[c] Complete dup 5p: number of cases, who presented these features out of the following six cases: Leshot and Lim, 1979; Kunze et al., 1980; Carnevale et al., 1982; Orye et al., 1983; Fujita et al., 1994; Zhao et al., 1995. Old cases without GTG bands and those with other possible aberrations in the implicated chromosomes have not been included.

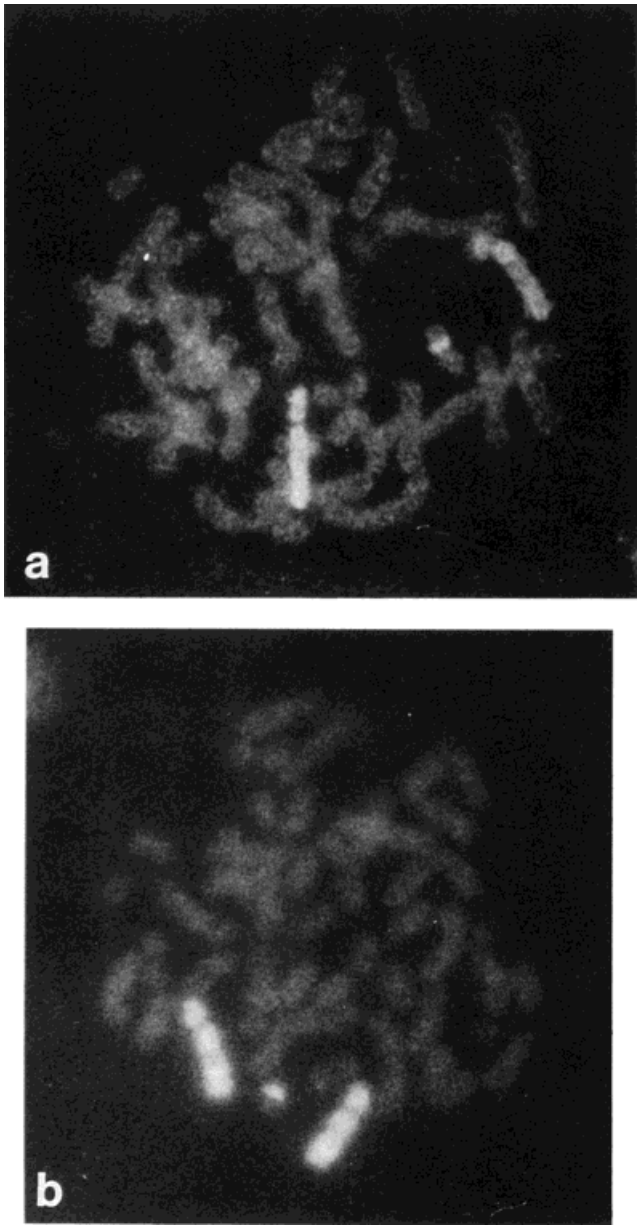

Fig. 3. (**a**) Maternal and (**b**) proband's metaphases stained by FISH with a library for chromosome 5, showing the insertion of material of chromosome 5 on chromosome 19.

clinical finding of dup(5p) were observed (Table I). A further precise delimitation of the critical subbands involved in the severe clinical manifestations of 5p duplications is difficult by conventional cytogenetic, but it should be feasible by a molecular approach.

Leichtman et al. [1991] described a patient with duplication 5pter→p12 and a pattern of congenital anomalies consistent with Opitz GBBB syndrome. They postulated that the dup(5p) syndrome might coincide with the GBBB syndrome. Although there are some similarities, specially in facial traits (hypertelorism, epicanthus, micrognathia) and in some other clinical manifestations (low-pitched cry, feeding and respiratory difficulties), findings such as hypospadias or laryngeal clefts, which are typical of the GBBB syndrome were found only in the dup (5p) case reported by Leichtman et al. [1991]. Recently, the Opitz GBBB syndrome was associated with other chromosomal abnormalities [McDonald-McGinn et al., 1995; Urioste et al., 1995; Verloes et al., 1995], suggesting genetic heterogeneity.

Most 5p duplications have arisen from parental chromosomal rearrangements, including inversions [Warter et al., 1973], reciprocal translocations [Yunis et al., 1978; Zabel et al., 1978], translocations onto acrocentric chromosomes [Vowles et al., 1984], intrachromosomal insertions [Webb et al., 1988; Rethoré et al., 1989], or interchromosomal insertions [Gustavson et al., 1988; Kunze et al., 1980], as in the present case. Insertional translocations, which are thought to be the result of three chromosome breakages, are rare. Although chromosome 5 is frequently involved in this kind of aberrations, no hot spots for breakage have been found in this chromosome [Abuelo et al., 1988; Van Hemel et al., 1995]. However, the two 5p duplications due to insertional translocations involving the centromere of chromosome 5 [Kunze et al., 1980; present case] and the preferential participation of chromosome 5 in isochromosome formation [Fujita et al., 1994] and whole arm translocations [Farrel and Fan 1995], might suggest a nonrandom propensity for breakage and reunion of chromosome 5 centromere.

ACKNOWLEDGMENTS

This work was supported in part by a grant from Consejería de Salud de la Comunidad Autónoma de Madrid, Spain. We appreciate the technical assistance of Teresa Lopez and Cándida Calderón.

REFERENCES

Abuelo DN, Barsel-Bowers G, Richardson A (1988): Insertional translocations: Report of new families and review of the literature. Am J Med Genet 31:319–329.

Brimblecombe FSW, Lewis FJ, Vowles M (1977): "Complete 5p" trisomy: 1 case and 19 translocation carriers in 6 generations. J Med Genet 14:271–275.

Carnevale A, Hernandez M, Limon-Toledo I, Frías S, Castillo J, del Castillo V (1982): A clinical syndrome associated with dup (5p). Am J Med Genet 13:277–283.

Chen H, Hoffman WH, Kusyk CJ, Tuck-Muller CM, Hoffman MG, Davis LS (1995): De novo dup (5p) in a patient with congenital hypoplasia of the adrenal gland. J Med Genet 55:489–493.

Chia NL, Bousfield LR, Johnson BH (1987): A case report of a de novo tandem duplication (5p)(p14-pter). Clin Genet 31:65–69.

Farrel SA, Fan YS (1995): Balanced nonacrocentric whole-arm translocations: A de novo case and literature review. Am J Med Genet 55:423–426.

Fujita M, Flori E, Lemaire F, Casanova R, Astruc D (1994): A new case of "complete" trisomy 5p with isochromosome 5p associated with a de novo translocation t(5;8)(q11;p23). Clin Genet 45:305–307.

Gustavson KH, Lundberg PO, Nicol P (1988): Familial partial trisomy 5p resulting from segregation of an insertional translocation. Clin Genet 33:404–409.

Kleczkowska A, Fryns JP, Moerman P, Vandenberghe K, Vandenberghe H (1987): Trisomy of the short arm of chromosome 5: Autopsy data in a malformed newborn with inv dup (5) (p13.1–p15.3). Clin Genet 32:49–56.

Kunze J, Johs R, Tolksdorf M (1980): Totale Trisomie 5p bei mütterlicher balancierter Translocation: 46,XX inv ins (1;5)(p32 oder 34;pter p11). Klinische Genetik in der Pädiatrie 2. Stuttgart: Thieme, pp. 201–202.

Leichtman LG, Werner A, Bass WT, Smith D, Brothman AR (1991): Apparent Opitz BBBG syndrome with a partial duplication of 5p. Am J Med Genet 40:173–176.

Lejeune J, Lafourcade J, Berger R, Turpin R (1964): Segregation familiale d'une translocation 5-13 déterminant une monosomie et une trisomie partielles du bras court du chromosome 5: Maladie de cri du chat et sa réciproque. CR Acad Sci (III)258:5767–5770.

Leschot NJ, Lim KS (1979): Complete trisomy 5p: De novo translocation t(2;5)(q36;p11) with isochromosome 5p. Hum Genet 46:271–278.

McDonald-McGinn DM, Driscoll DA, Bason L, Christensen K, Lynch D, Sullivan K, Canning D Zavod W, Quinn N, Rome J, Paris Y, Weinberg P, Clark BJ, Emanuel BS, Zackai EH (1995): Autosomal dominant "Opitz GBBB" Syndrome due to a 22q11.2 deletion. Am J Med Genet 59:103–113.

Orye E, Benoit Y, Van Mele B (1983): Complete trisomy 5p owing to de novo translocation t(5;22)(q11;p11) with a familial pericentric inversion of chromosome 2, inv 2 (p21q11). J Med Genet 20:394–395.

Rethoré MO, De Blois MC, Peeters M, Popowski P, Pangalos C, Lejeune J (1989): Pure partial trisomy of the short arm of chromosome 5. Hum Genet 82:296–298.

Rogne S, Myklebost O, Olving JH, Kyrkjebo HT, Jonassen R, Olaisen B, Gedde-Dahl T Jr (1991): The human genes for complement components 6 (C6) and 9 (C9) are closely linked on chromosome 5. J Med Genet 28:587–590.

Urioste M, Arroyo I, Villa A, Lorda-Sanchez I, Barrio R, Lopez-Cuesta MJ, Rueda J (1995): Distal deletion of chromosome 13 in a child with the "Opitz" GBBB syndrome. Am J Med Genet 59:114–122.

Van Dyke DL (1988): Isochromosomes and interstitial tandem direct and inverted duplications. In: Daniel A, ed. "The Cytogenetics of Mammalian Autosomal Rearrangements." New York: Alan R. Liss, pp 635–665.

Van Hemel JO, van der Heide GA, Eussen HJ (1995): Interchromosome insertional translocation: Report of four new cases. Chrom Res 3 (Supplement 1):P14.

Verloes A, David A, Odent S, Toutain A, Andre MJ, Lucas J, Le Marec B (1995): Opitz GBBB syndrome: Chromosomal evidence of an X-linked form. Am J Med Genet 59:123–128.

Vowles M, McDermtt A, Janota I (1984): Trisomy 5p; a second case occurring in a previously described kindred. J Med Genet 21:144–156.

Warter S, Ruch JV, Lehmann M (1973): Karyotype with chromosomal abnormality with various inherited defects in the offspring (recombinant aneusomy). Hum Genet 20:355–359.

Webb GC, Voullaire LE, Rogers JG (1988): Duplication of a small segment of 5p due to maternal recombination within a paracentric shift. Am J Med Genet 30:875–881.

Yunis E, Silva R, Egel H, Zuñiga R, Torres de Caballero OM, Ramirez E, Poveda de Ruiz H (1978): Partial trisomy 5p. Hum Genet 43:231–237.

Zabel B, Baumann JG, Conrad G (1978): Partial trisomy for short and long arm of chromosome n°5. Two cases of two possible syndromes. J Med Genet 15:143–147.

Zenger-Hain JL, Vandyke DL, Wiktor A, Walker H, Feldman GL (1993): Inverted duplication of chromosome 5p14p–p15.3 confirmed with in situ hybridization. Am J Med Genet 47:1198–1201.

Zhao J, Gordon PL, Wilroy RS Jr, Martens PR, Tarleton J, Shulman LP, Simpson JL, Elias S, Tharapel AT (1995): Characterization of an unbalanced de novo rearrangement by microsatellite polymorphism typing and by fluorescent in situ hybridization. Am J Med Genet 56:398–402.